# Epitomes

## Important Advances in Clinical Medicine

# Pathology

*The Scientific Board of the California Medical Association presents the following inventory of items of progress in pathology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers, or scholars to stay abreast of these items of progress in pathology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.*

*The items of progress listed below were selected by the Advisory Panel to the Section on Pathology of the California Medical Association and the summaries were prepared under its direction.*

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## Platelet Antibodies

THROMBOCYTOPENIA may occur as the sole manifestation of disease or may be due to another disorder. The management of either primary or secondary thrombocytopenia depends on correctly identifying the causal pathophysiologic processes. Over the past decade a number of research laboratories have provided data to strongly support the hypothesis that primary isolated thrombocytopenia in adults—idiopathic thrombocytopenia purpura—is immune-mediated and in many cases may be more correctly termed autoimmune thrombocytopenia purpura. The development of sensitive assays that directly measure platelet-associated immunoglobulin (PAIg) corroborated earlier studies which suggested that this disorder is due to the deposition of immunoglobulin on the platelet surface, leading to the accelerated clearance of sensitized platelets. The ability to directly measure PAIg, in contrast to the earlier tests for detecting serum antiplatelet factors, has increased the sensitivity from 60% to greater than 90% with 93% specificity for detecting immune-mediated platelet destruction.

The increased diagnostic sensitivity has raised new questions concerning the specificity of elevated PAIg levels. It is now well recognized that increased PAIg can occur in thrombocytopenia associated with a wide variety of disorders, including systemic lupus erythematosus, lymphoma, carcinoma, Hodgkin's disease, the acquired immunodeficiency syndrome, and Hashimoto's thyroiditis. Elevated PAIg levels also may be associated with qualitative platelet dysfunction without concurrent thrombocytopenia. Thus, elevated PAIg levels are not specifically associated with isolated autoimmune or idiopathic thrombocytopenia purpura. In most cases, it is unclear whether PAIg noted in either autoimmune thrombocytopenia purpura or the secondary disorders is specifically directed against a platelet antigen or is nonspecifically deposited on the platelet surface as part of an immune complex. In several recent reports the use of immunoblot techniques has identified PAIg directed against integral platelet proteins in some patients with autoimmune thrombocytopenia purpura. A recent study using monoclonal reagents for the detection of cell-associated immunoglobulin has provided stronger evidence that the presence of elevated levels of PAIg—more than 800 molecules of IgG per platelet—is physiologically consistent with currently understood immune-mediated clearance of other blood cells, and this concentration of cell-associated immunoglobulin is not observed in patients with nonimmune thrombocytopenia.

Each of the different techniques described to measure PAIg requires isolating platelets from whole blood, which may be difficult in patients with severe thrombocytopenia. Newly described fluorescence-activated flow cytometric assays and radioactive immunologic assays, however, exhibit adequate sensitivity even when few platelets are available. Indirect tests may be useful to diagnose neonatal isoimmune thrombocytopenia, post-transfusion purpura, or transfusion-induced alloimmunization. Indirect assays for determining suspected drug-dependent immune thrombocytopenia have had disappointing results due to the inability to solubilize drugs and do the assays under physiologic conditions. In summary, the direct measurement of platelet-associated immunoglobulin is useful in establishing the diagnosis of immune-mediated platelet destruction and in choosing among various therapeutic alternatives during the course of these disorders.

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## Fine-Needle Aspiration Biopsy of Lymph Nodes

FINE-NEEDLE ASPIRATION (FNA) or aspiration biopsy cytology of lymph nodes is done in patients presenting with persistent lymphadenopathy for which no obvious explanation exists, to stage patients with previously diagnosed malignancy (including malignant lymphoma), and to monitor for recurrence and progression of disease. Within this setting, a diagnosis of infection, reactive hyperplasia, malignant lymphoma, and metastatic tumor is sought.

The diagnosis of metastatic carcinoma usually is straightforward, as is the diagnosis of many reactive, inflammatory, and granulomatous disorders. The use of lymph node FNA for the primary diagnosis of malignant lymphoma has proved

more challenging. For this reason, a confirmatory surgical biopsy is done at most hospitals in which a cytologic diagnosis of malignant lymphoma has been made or is suspected. This may not be necessary in selected cases at centers with broad experience in the diagnosis of lymphoproliferative disorders, especially when ancillary marker studies are available to confirm the cytologic interpretation.

One argument for following lymph node FNA with a biopsy is to assess a nodular or diffuse pattern of infiltration, a distinction that carries therapeutic and survival implications based on the grading system enumerated in the National Cancer Institute (NCI) working formulation for non-Hodgkin's lymphomas.

Surgical biopsy must be done in cases of malignant lymphoma of predominantly small cleaved cell type (poorly differentiated lymphocytic lymphoma) and in cases of malignant lymphoma of mixed small cleaved and large cell type. Because these lymphomas show a spectrum of cell size, they may present a diagnostic problem on aspiration biopsy. Furthermore, they are classified as either low-grade or intermediate-grade lymphomas based on the biopsy assessment of a nodular or diffuse pattern. Malignant lymphoma of small lymphocytic cell type (well-differentiated lymphocytic lymphoma), chronic lymphocytic leukemia, and malignant lymphoma of small lymphocytic-plasmacytoid type are low-grade malignant disorders but are difficult to diagnose unequivocally without the benefit of biopsy or ancillary marker studies. On the other hand, a biopsy would not be necessary to grade malignant lymphomas of large cell type, which are classified as intermediate grade whether nodular or diffuse. Large cell malignant lymphoma; malignant lymphoma, immunoblastic (immunoblastic sarcoma); malignant lymphoma, lymphoblastic (convoluted and nonconvoluted T-cell lymphoma); and malignant lymphoma of small noncleaved cells (Burkitt's) are all high-grade lymphomas according to the NCI working formulation and represent lymphomas that can be diagnosed by fine-needle aspiration.

Although centers with expertise in hematologic disorders may not require a confirmatory surgical biopsy in the FNA diagnosis of several types of malignant lymphoma, hospitals that have limited experience in this discipline should continue to use confirmatory surgical biopsy for diagnostic accuracy rather than relying on aspiration cytology alone.

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## Biopsy Findings in Liver Transplant Patients

IN THE PAST FEW YEARS, orthotopic liver transplantation has become a relatively common therapy for a wide variety of both pediatric and adult liver diseases. Despite improved surgical and immunosuppressive techniques, patients undergoing this procedure are vulnerable to numerous complications involving transplantation-associated injury to the donor organ, infection exacerbated by immunosuppression, biliary obstruction or leaks, vascular occlusion, and acute and chronic rejection. Liver biopsy has been shown to be an important adjunct to radiologic and serologic studies in these patients and is essential in discriminating between rejection and ischemic injury, two of the most common causes of graft dysfunction, as well as sometimes identifying viral infections in these immunosuppressed patients.

Acute rejection is histologically characterized by a mixed inflammatory infiltrate of the portal tracts composed primarily of T cells but with significant proportions of plasma cells, neutrophils, and eosinophils as well. These inflammatory cells are frequently found intimately associated with the epithelial cells lining the small interlobular bile ductules and the endothelial cells of the portal and centrilobular blood vessels (endotheliitis). This association is believed to be due to the stronger expression of major histocompatibility complex antigens by the bile duct and endothelial cells when compared with the hepatocytes. As a consequence, in most cases of rejection the bile ductules will show evidence of injury or regeneration while hepatocyte necrosis is not a prominent feature. Biliary epithelial injury can occasionally become so severe that most of the ductules will be completely destroyed over a long-term course ("vanishing duct syndrome"), a condition usually requiring retransplantation. Chronic injury to the liver vasculature has also been reported, with arteriolar thickening, fibrointimal hyperplasia of the large arteries, and the accumulation of subintimal foam cells in the hilar vessels with partial occlusion.

Ischemic injury to the liver is the second most common source of acute graft dysfunction and manifests four basic patterns on liver biopsy—focal infarcts, massive centrilobular necrosis, diffuse individual hepatocyte necrosis, and centrilobular hepatocyte ballooning. Focal infarcts occur as a result of ischemia of a specific portion of the liver either perioperatively or from postoperative vascular occlusion. They can vary in size and distribution, histologically showing confluent tissue necrosis with adjacent viable tissue; because of the focal nature of this lesion, a single liver biopsy may not detect it. The clinical sequelae of infarction depend on its extent and whether the necrotic tissue becomes secondarily infected.

Generalized, massive centrilobular necrosis is the result of diffuse liver injury, such as severe hypotension; this histologic finding usually leads to retransplantation. Diffuse, scattered, individual hepatocyte necrosis without inflammation is also a pattern of generalized ischemic injury, and depending on the severity of the insult there may be only a few necrotic cells within the lobule or numerous necrotic cells followed within three days by generalized graft destruction. Less severe generalized ischemic injury results in centrilobular hepatocyte "ballooning" in which liver cells around the central vein become notably swollen, with clear, "hydropic" cytoplasm. In most cases this swelling resolves without sequelae; in severe cases, however, there may be eventual centrilobular hepatocyte loss followed by pronounced cholestasis without apparent duct obstruction.

Viral infection clinically mimicking rejection or ischemia can be detected by biopsy in many cases. The most common virus is cytomegalovirus, but herpesvirus, adenovirus, and hepatitis B virus have also been described. Characteristic viral inclusions or patterns of necrotic hepatocytes in association with inflammatory cells are clues to viral infection. Immunohistochemical stains and DNA hybridization studies